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New Insights Into the Phenotypes of 6q Deletions

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Deletions of chromosome 6q are rare. We report 3 new patients with 6q deletions. Case 1 is a male with an interstitial deletion [del(6)(q13q14.2)], hypotonia, speech delays, and minor anomalies. Case 2 is a male with an interstitial deletion [del(6)(q16.2q22.32)] and malformations, including truncus arteriosus and bilateral oligodactyly. Case 3 is a male with a terminal deletion [del(6)(q25.2)] with retinal pits, hydrocephalus, atrioventricular canal, and hydronephrosis. The findings in our patients and those from 57 previously reported cases demonstrated 3 phenotypic groups associated with 6q deletions. Group A [del(6)(q11-q16)] had a high incidence of hernias, upslanting palpebral fissures, and thin lips with lower frequency of microcephaly, micrognathia, and heart malformations. Group B [del(6)(q15-q25)] was associated with increased intrauterine growth retardation, abnormal respiration, hypertelorism, and upper limb malformations. Group C [del(6)(q25-qter)] was associated with retinal abnormalities, cleft palate, and genital hypoplasia. The only universal finding among all patients with 6q deletions was mental retardation. Other findings common to all 3 groups included ear anomalies (90%), hypotonia (82%), and postnatal growth retardation (68%). Am. J. Med. Genet. 70:377–386, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: chromosome 6; deletion, mental retardation; recognizable phenotype; multiple anomalies; limb malformation; cardiac anomaly

INTRODUCTION

Despite 57 case reports of deletions of the long arm of chromosome 6, there is little indication in the literature of phenotypic correlations with deletions of specific regions of chromosome 6q [Bartoshesky et al., 1978; Bzdúch and Lukáčová, 1989; Chery et al., 1989; Cote et al., 1981; Dallapiccola et al., 1978; DiLernia and Albertini, 1994; Fryns et al., 1986, 1991; Gershonibaruch et al., 1996; Glover et al., 1988; Goldberg et al., 1980; Hagameijer et al., 1977; Horigome et al., 1991; Ito et al., 1989; Kassikoff and Sekhon, 1990; Kueppers et al., 1977; Liberfarb et al., 1978; Lonardo et al., 1988; Matkins et al., 1985; McLeod et al., 1990; McNeal et al., 1977; Meng et al., 1992; Mikkelsen et al., 1973; Milošević and Kaličanin, 1975; Nakagome et al., 1980; Narahara et al., 1991; Oliveira-Duarte et al., 1990; Pandya et al., 1995; Park et al., 1988; Rivas et al., 1986; Roland et al., 1993; Romie et al., 1996; Rose et al., 1992; Scarsbrough et al., 1984; Schwartz et al., 1984; Shen-Schwartz et al., 1989; Schnizel, 1984; Slate et al., 1987; Stevens et al., 1988; Tajara et al., 1990; Tranebjaerg et al., 1986; Turleau et al., 1988; Valtat et al., 1992; Villa et al., 1995; Wakahama et al., 1991; Warburg et al., 1991; Yamamoto et al., 1986; Young et al., 1985]. We report on 3 patients with deletions of 6q whose deletions do not overlap. There are significant phenotypic differences among these patients. 57 previously reported cases are reviewed in order to clarify the phenotype/karyotype correlations of 6q deletions.

CLINICAL REPORTS

Case 1

A 3-year-old Japanese boy was referred to the Division of Human Genetics for hypotonia and speech delays. He was the product of an uncomplicated term pregnancy to a 35-year-old gravida 2, para 2 woman and her 34-year-old partner. There were no unusual exposures during the pregnancy and no perinatal problems. Birth weight was 2.415 kg (10th centile). He had an umbilical hernia. Hypotonia and developmental delays were noted at 7 months. An MRI scan of the brain was normal at 18 months. Karyotype in Japan at 18 months was reportedly normal. He started scooting when prone at age 2 years. At the time of our evaluation at age 3 years he could walk with support. He had no speech and minimal receptive language skills. Oc-

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cupational therapy evaluation demonstrated delayed functioning at the 1st or 2nd centile for age.

On physical examination his weight was 11.1 kg (<5th centile), height 85 cm (<5th centile), and OFC 49.5 cm (40th centile). He had hypertelorism, upslanting palpebral fissures, bilateral epicanthic folds, flat nasal bridge, and thin lips. The ears were large and apparently low-set (Fig. 1). Cardiac findings and genitalia were normal. Bridging palmar creases were noted bilaterally. He was markedly hypotonic.

The family history was unremarkable. He has a normal 5-year-old sister.

High resolution chromosome analysis showed an interstitial deletion of the proximal portion of the long arm of chromosome 6, 46XY,del(6)(q13q14.2) (Fig. 2). Chromosomes of parents and sister were normal.

Case 2

A boy was born at 39 weeks of gestation to a 25-year-old gravida 1 white woman and a 27-year-old man. The pregnancy was complicated by a *Trichomonas* infection treated with metronidazole at 16 weeks. Labor was induced at 39 weeks because of intrauterine growth retardation. There was no history of alcohol, tobacco, or drug exposure. Delivery was by cesarean section for fetal distress. Apgar scores were 6 at 1 minute, and 7 at 5 minutes.

Birth weight was 2.110 kg (<5th centile), length 38 cm (<5th centile), OFC 29 cm (<5th centile). The patient was cyanotic and had a weak, high-pitched cry. He also had brachycephaly, high broad forehead, delicate facial structure, apparently low-set simple ears, right preauricular sinus, short palpebral fissures, hypertelorism, bulbous nasal tip, mild retro/micrognathia, and high arched palate with wide lateral palatine ridges (Figs. 3, 4). There was no heart murmur. The phallus was normal; however, the scrotum was small with right cryptorchidism. The left arm was short with a flexion contracture at the elbow. There was a single bone in the left forearm, and a single digit on the left hand (Fig. 5). The left shoulder had limited abduction. The right hand had only 4 digits with partial syndactyly of digits 2–3; digit 2 had no nail; digits 3 and 4 had abnormal nails. All fingers were markedly tapered (Fig. 6). There were rocker bottom feet, short toes with hypoplastic nails, and dorsi flexed great toes.

Echocardiogram demonstrated truncus arteriosus. Chest radiograph showed a bifid thoracic vertebra at T5. Renal ultrasound findings were normal. Cranial ultrasound study showed subependymal cysts. Auditory evoked response testing disclosed bilateral profound sensorineural hearing loss. Ophthalmological findings were normal. Chromosomal analysis showed an interstitial deletion of 6q; the karyotype was 46,XY,del(6)(q16.2q22.32)mat (Fig. 7).

The family history was unremarkable. Chromosome

Fig. 1. Case 1 at 3 years. Note large mildly abnormal ears, and relatively normal appearance.

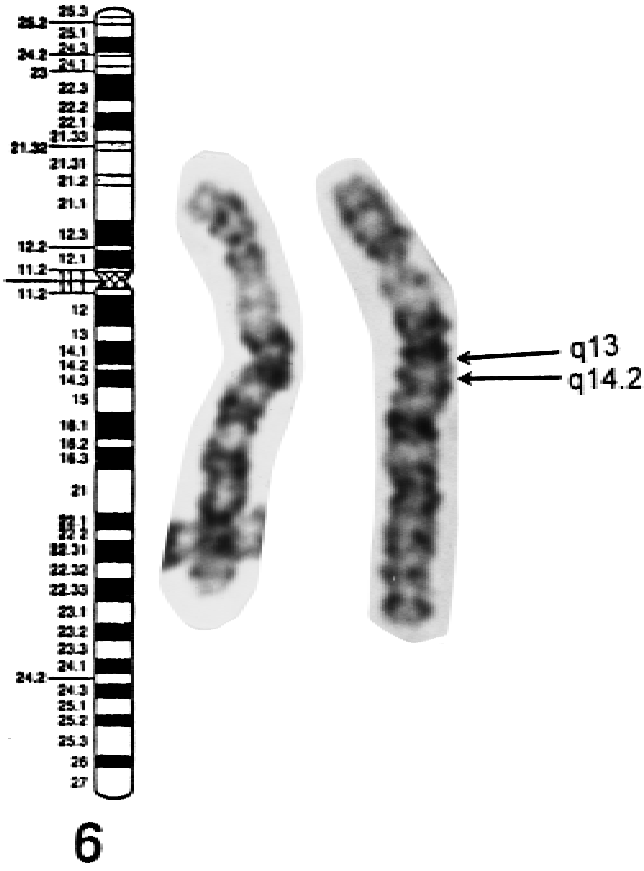

Fig. 2. Idiogram of chromosome 6 and partial karyotype from case 1; the normal chromosome 6 homologue is on the right demonstrating the deleted segment.

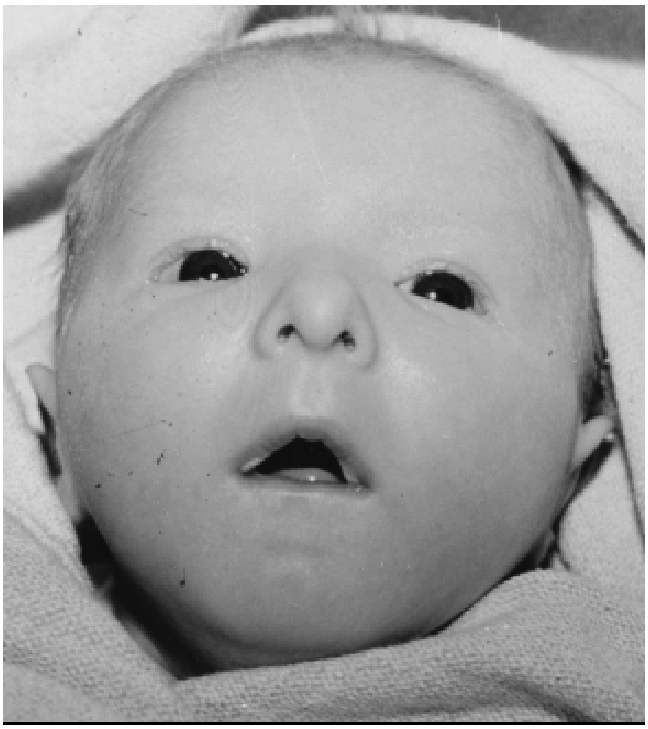

Fig. 3. Case 2 at 9 months. Note high broad forehead, short palpebral fissures, small mouth, and lack of facial expression.

analysis of the patient's mother documented an apparently balanced translocation with karotype 46,XX,dir ins(2;6)(q14.2;q16.2q22.32) (Fig. 8). The father had normal chromosomes.

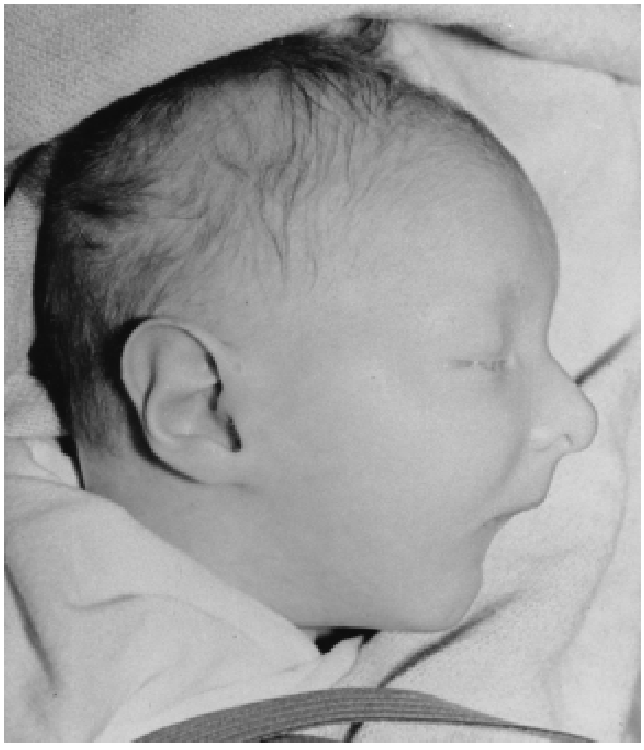

Fig. 4. Profile of case 2 at 9 months. Note simple ears, prominent nose, and retrognathia.

Fig. 5. Left upper limb of case 2.

The patient required prolonged mechanical ventilation for respiratory distress, and was treated for necrotizing enterocolitis. Fundoplication and a gastrostomy tube placement for gastroesophageal reflux were performed on day 36. He had intermittent episodes of central apnea and pulmonary edema that were not explained by his cardiac disease. The cardiac malformation was repaired at another institution at age 3 months. He developed bacterial and candidal sepsis, and remained on mechanical ventilation for 2 months after the cardiac surgery. At 7 months an anomalous subclavian artery compressing the trachea and laryngotracheomalcia were discovered. He continued to have respiratory distress and periodic apneic episodes at age 9 months. At 10 months he responded to visual and tactile stimuli by kicking his feet and occasionally smiling or grimacing. At 11 months he developed seizures. He gained few other skills, and continued to require intensive care until age 16 months when he became apneic and died while sleeping. Autopsy was not performed.

Case 3

A boy was born at 39 weeks of gestation to a 19-year-old gravida 1 white woman. The pregnancy was com-

Fig. 6. Right hand of case 2. Only 4 digits with no flexion creases in the 4th digit. There is partial syndactyly of digits 2–3.

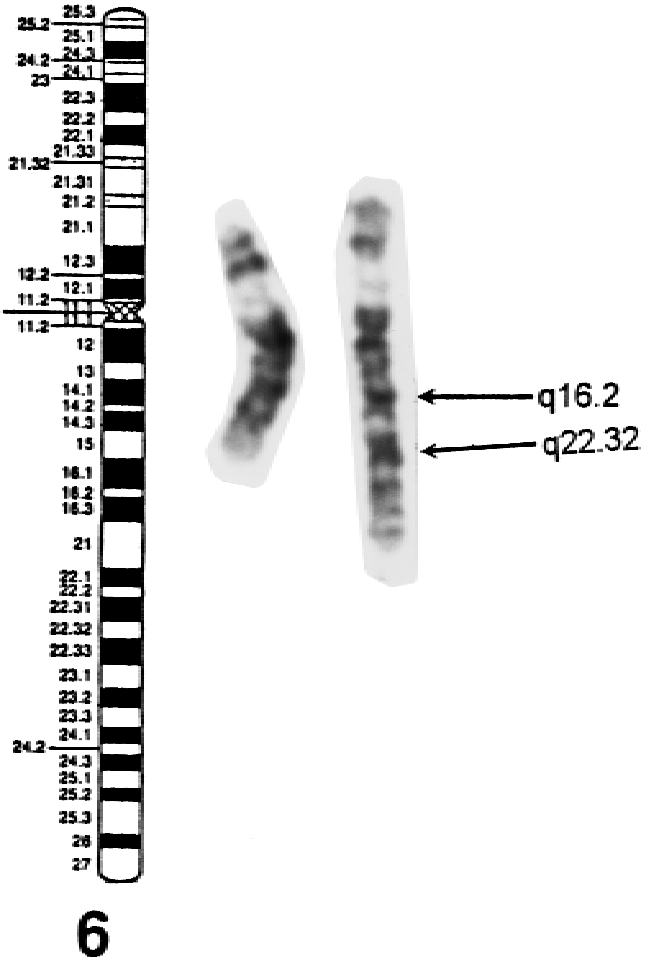

Fig. 7. Idiogram of chromosome 6 and partial karyotype case 2 with normal chromosome 6 homologue on the right illustrating the deleted segment.

plicated by lack of prenatal care and maternal use of alcohol and cocaine. Delivery was complicated by fetal distress requiring cesarean section and the presence of thick meconium. Apgar scores were 4 at 1 minute, and 7 at 7 minutes.

Birth weight was 2.6 kg (10th centile), length 55.5 cm (5th centile), OFC 44 cm (>95th centile). He had a capillary hemangioma on the nasal tip extending to the philtrum. The anterior fontanel was wide and full. Palpebral fissures were straight. He had lacrimal duct stenosis, telecanthus, prominent nasal bridge, broad nasal tip, and anteverted nares. The ears were mildly abnormal, posteriorly angulated and apparently low-set. A preauricular sinus was present bilaterally. The philtrum was long, but well formed (Figs. 9, 10). The palate was normal. There was redundant nuchal skin. A II/VI systolic murmur was heard on auscultation. The liver edge was palpable 5 cm below the right costal margin. Genitalia were normal. A deep sacral pit was present. There was no Moro response. He was hyperresponsive to touch, but failed to respond to auditory or visual stimuli. He was hypotonic centrally with increased appendicular tone.

Further evaluation demonstrated hydrocephalus and ventriculoseptal defect with pulmonary valve stenosis. Dilated eye examination showed retinal pits and macular hypoplasia. Auditory evoked response was consistent with severe sensorineural hearing loss. Hydronephrosis was demonstrated with abdominal ultrasound.

A ventriculoperitoneal shunt was placed to control the hydrocephalus. Hearing aids were prescribed with little success. No attempt was made to correct the cardiac malformation. Over the next two years he suffered from multiple infections, including pneumonia, otitis media, and *Staphylococcus aureus* meningitis. He required oxygen supplementation throughout his life. He suffered from congestive heart failure and asthma. His development was profoundly delayed. He first rolled over at 13 months, and made little progress beyond that. He required gastrostomy feedings secondary to dysphagia. He died of respiratory failure secondary to pulmonary hypertension shortly after his second birthday.

Chromosome study documented a terminal deletion of 6q, 46,XY,del(6)(q25) (Fig. 11). The parents' chromosomes could not be studied.

DISCUSSION

We have described 3 cases of partial deletion of the long arm of chromosome 6. Each patient has different clinical signs, depending on the location and extent of the deletion.

Although limb anomalies have been reported with 6q deletions, severe limb malformations have been rare. Case 2 had severe limb anomalies consisting of a single bone in the forearm with a single digit on the left (Fig. 5). The right side was less severely affected (Fig. 6). Similar limb malformations were reported with 6q deletions. Pandya et al. [1995] recently reported on 2 patients with deletions very similar to case 2 of this report who had limb ray defects. One of their patients had bilateral oligodactyly; the other had polydactyly of one hand with oligodactyly of the other. Viljoen and Smart [1993] reported on a patient with ectrodactyly and other anomalies who had an apparently balanced translocation involving chromosomes 6 and 13. The breakpoint on chromosome 6 was at 6q21. Goldberg et al. [1980] reported on a case with very unusual malformations of the hands consisting of non-ridged skin covering the ulnar third of each palm and the 4th and 5th fingers, dorsal and palmar nails on each 5th finger, and absent joint mobility of the 5th digits. One case of triphalangeal thumbs has also been described [Horigome et al., 1991]. The middle region of 6q apparently contains a gene or genes important in controlling limb morphogenesis. The critical region for this type of limb defect apparently falls between 6q21 and 6q23, probably near 6q21.

A wide variety of congenital heart malformations have been reported in patients with 6q deletions; however, truncus arteriosus, seen in our case 2 has not been reported previously.

In comparing the findings of our 3 patients with those of 57 previously reported patients with deletions of 6q, we grouped patients according to the presence or

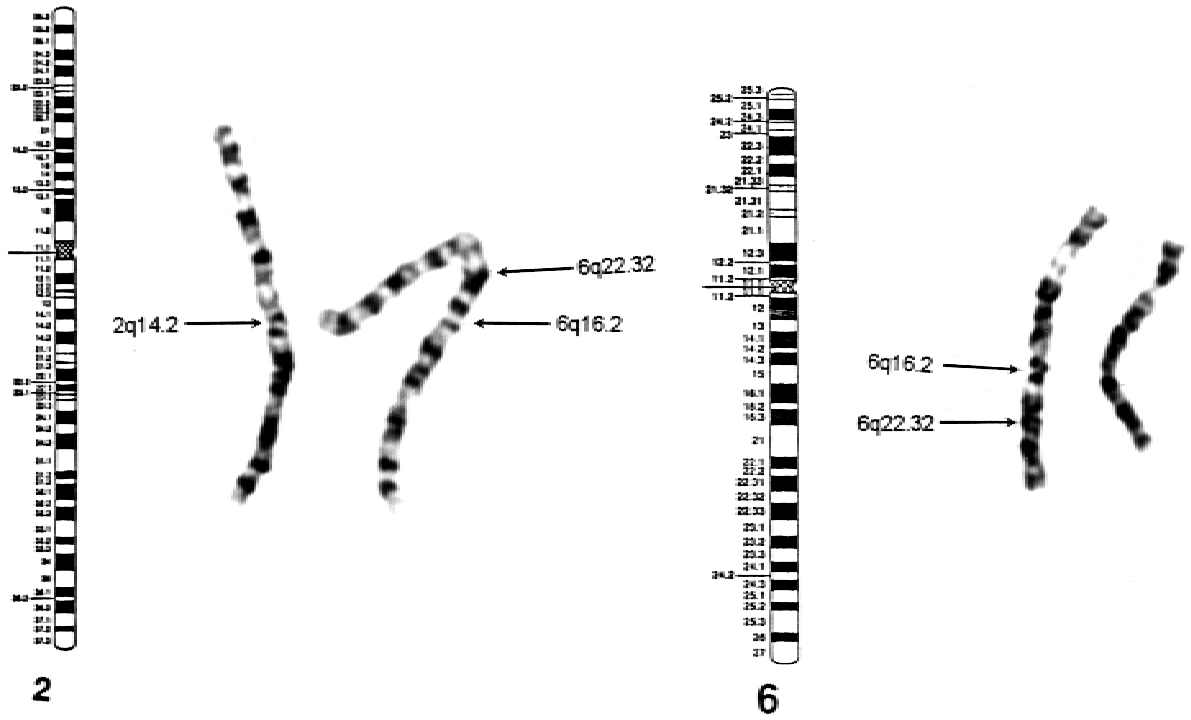

Fig. 8. Ideograms of chromosomes 2 and 6 with composite partial karyotype of chromosomes 2 and 6 from the mother of case 2. The chromosome 2 homologues are on the left. The normal homologue is demonstrated with the break point at 2q14.2. The inserted material from chromosome 6 is seen in the abnormal homologue. The homologues of chromosome 6 are on the right. The deleted homologue is compared to the normal (with breakpoints demonstrated).

absence of limb defects, congenital heart disease, genital malformations, retinal abnormalities, hernias, low birth weight, hypertelorism, and upslanting palpebral fissures. We noted that certain patients consistently grouped together. On further analysis 3 distinct phenotypes corresponding to the deleted region emerged: proximal deletions with breakpoints between 6q11 and 6q16 (group A), deletions with breakpoints between 6q15 and 6q25 (group B), and 6q25 to ter (group C); however, there was overlap between groups A and B for deletion of band 6q16. One reason for this overlap may

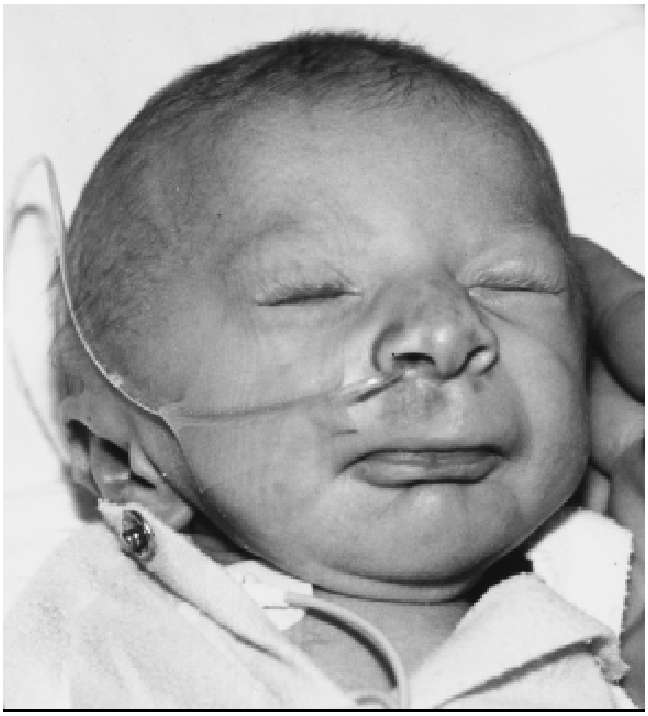

Fig. 9. Case 3 at 1 month. Note bulbous nasal tip, low set posteriorly angulated ears, preauricular sinus, short palpebral fissures, and facial hemangioma.

Fig. 10. Profile of case 3 at 1 month. Note sloping forehead, apparently low set abnormal ear, and retrognathia.

TABLE I. Percentages of Patients With Reported Characteristics*

	Total	Group A	Group B	Group C
Reported characteristics	% (60)	% (14)	% (19)	% (26)
Mental retardation	100 (50)	100 (13)	100 (15)	100 (21)
Ear anomalies	90 (57)	83 (12)	100 (18)	88 (25)
Hypotonia	84 (39)	90 (10)	76 (13)	86 (15)
Limb anomalies	70 (57)	78 (14)	64 (17)	71 (25)
Microcephaly	67 (52)	38 (13)	75 (16)	82 (22)
Dermatoglyphics	69 (35)	100 (9)	56 (9)	62 (16)
Growth failure	67 (51)	83 (12)	62 (16)	61 (21)
Broad nasal tip	57 (56)	57 (14)	64 (17)	50 (24)
Prominent nasal bridge	56 (56)	50 (14)	41 (17)	67 (24)
Micrognathia	59 (58)	36 (14)	61 (18)	72 (25)
Epicanthal folds	57 (57)	64 (14)	37 (18)	66 (24)
Brain anomalies	56 (40)	33 (10)	57 (14)	67 (16)
Cranial abnormalities	47 (60)	36 (14)	63 (19)	52 (25)
Short neck	46 (57)	43 (14)	39 (18)	58 (25)
Cardiac anomalies	43 (57)	28 (14)	50 (18)	48 (24)
Eye anomalies	46 (56)	42 (14)	44 (18)	50 (23)
High arched palate	47 (48)	42 (12)	70 (17)	28 (17)
Hypertelorism	40 (53)	31 (13)	61 (18)	30 (21)
Long philtrum	42 (55)	50 (14)	24 (17)	55 (23)
Low birth weight	38 (53)	28 (14)	60 (15)	28 (24)
Upslanting palpebral fissures	40 (55)	86 (14)	22 (18)	24 (22)
Genital anomalies	37 (60)	14 (14)	37 (19)	48 (26)
Respiratory abnormalities	29 (56)	21 (14)	42 (17)	20 (24)
Gastrointestinal anomalies	27 (57)	30 (13)	11 (18)	24 (25)
Mouth anomalies	27 (54)	21 (14)	35 (17)	23 (23)
Hernia(s)	27 (55)	71 (14)	11 (18)	16 (25)
Downslanting palpebral fissures	24 (55)	0 (14)	39 (18)	29 (22)
Thin lips	26 (55)	57 (14)	11 (17)	14 (23)
Flat nasal bridge	22 (56)	21 (14)	30 (17)	16 (25)
Seizures	21 (54)	0 (13)	11 (17)	38 (23)
Scoliosis	21 (58)	21 (14)	22 (17)	21 (25)
Chest wall anomalies	20 (60)	21 (14)	16 (19)	24 (26)
Infant mortality	19 (57)	0 (14)	27 (18)	12 (24)
Prominent forehead	19 (57)	0 (14)	33 (18)	22 (23)
Hypertonia	18 (39)	10 (10)	15 (13)	29 (15)
Short palpebral fissures	21 (56)	28 (14)	28 (18)	14 (23)
Abnormal hair pattern	17 (54)	7 (14)	6 (16)	30 (24)
Hyper extensible joints	15 (52)	25 (12)	6 (17)	14 (22)
Renal anomalies	17 (54)	23 (13)	12 (16)	17 (23)
Vertebral anomalies	13 (55)	15 (13)	18 (16)	8 (25)

*Numbers without parenthesis indicate percent; numbers in parenthesis indicate number of patients with adequate information for analysis.

be an apparent increase in breakpoints at 6q15 (10 patients 5 from group A and 5 from group B). The distinction between these two groups seems to be determined more by the distal breakpoint than the more proximal one. There are also several patients with deletions overlapping two groups [Dallapiccola et al., 1978; Fryns et al., 1986; Goldberg et al., 1980; Ito et al., 1989; Kueppers et al., 1977; Meng et al., 1992; Shen-Schwartz et al., 1989; Tajara et al., 1990; Wakahama et al., 1991]. These patients generally had phenotypes with characteristics from each of the involved groups, but were generally more similar to the group that included the more distal breakpoint. It is interesting to note that the terminal deletions have some findings that are quite specific and the most proximal deletions are associated with relatively few malformations or minor anomalies. Thus, in deletions of 6q, the findings tend to be more striking and specific with more distal breakpoints.

An attempt was made to determine critical regions for various specific findings. This was largely unsuccessful. It was rarely possible to define a critical region since many abnormalities occurred in all groups but seemed to be more frequent in certain regions. Specific findings are discussed in association with each phenotypic group.

Analysis of more than 40 findings was done for each patient or case report. We compared the number of patients reported with each finding in each group and for the entire chromosome (see Table I). Several findings were commonly reported for patients in all 3 groups. Not surprisingly, mental retardation was found in all patients, with most being severely to profoundly retarded. Only 1 patient was documented to have mild mental retardation [Scarsbrough et al., 1984]. External ear abnormalities were reported in 90% of cases on whom there were adequate descriptions. Ears were apparently low set, large, and/or malformed. Five of 9 patients who had formal hearing evaluations had significant hearing loss [Chery et al., 1989; Gershoni-baruch et al., 1996; McNeal et al., 1977; Milošević and Kaličanin, 1975; Pandya et al., 1995;

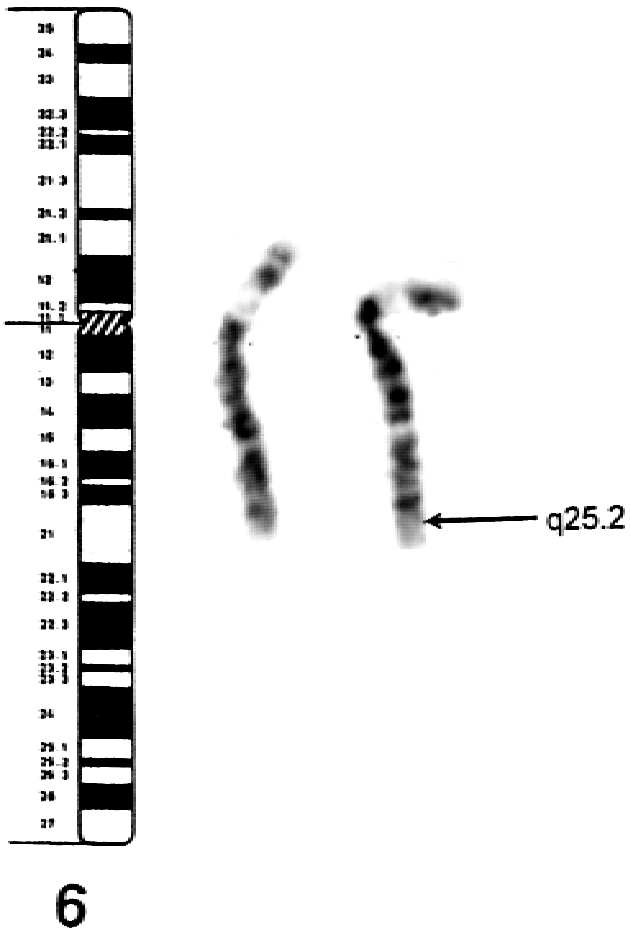

Fig. 11. Idiogram of chromosome 6 and partial karyotype of case 3. Normal homologue of chromosome 6 is on the right illustrating the terminal deletion.

Scarsbrough et al., 1984; Tranebjaerg et al., 1986]. There were two few patients to determine critical regions for deafness. Hypotonia was described in 84% of patients where tone was described, and was common to all 3 deletion groups. In most cases the hypotonia persisted. However, in 4 cases hypotonia progressed to hypertonia [Rivas et al., 1986; Schwartz et al., 1984; Stevens et al., 1988]. Four patients were hypertonic at the time of the first reported evaluation [Cote et al., 1981; Narahara et al., 1991; Roland et al., 1993; Stevens et al., 1988]. No mention of tone was made in 21 of the 57 cases. Table I summarizes findings reported with 6q deletions.

Deletions: 6q11 to 6q16 (Group A)

We reviewed 12 cases (including case 1) with proximal deletions of 6q [DiLernia and Albertini, 1994; Gershoni-baruch et al., 1996; Lonardo et al., 1988; McNeal et al., 1977; Roland et al., 1993; Romie et al., 1996; Rose et al., 1992; Slater et al., 1987; Turleau et al., 1988; Valtat et al., 1992; Yamamoto et al., 1986; Young et al., 1985]; 86% had upslanting palpebral fissures. This finding was also present in 23% of more distal deletions of 6q. In more distal deletions an equal number had downslanting palpebral fissures. Downslanting palpebral fissures were not seen in patients with deletions proximal to 6q16. Thin lips were reported in 57% of the patients in group A. Facial appearances were similar among patients and were not grossly abnormal. In fact, several patients, including case 1 (Fig. 1), were not felt to be abnormal at birth. Seventy-one percent (71%) of the patients in group A had umbilical or inguinal hernias. Hernias were reported in only 14% of patients with more distal 6q deletions. It is interesting to note that the alpha-1 subunit of type IX collagen has been mapped to 6q13 [Warman et al., 1993]. Abnormalities of collagen have been associated with increased risk of hernias in Elhers-Danlos syndrome and other connective tissue disorders. In addition 5 of 14 patients in group A had abnormalities of the skin reported. Three patients had club feet [Gershoni-baruch et al., 1996; Turleau et al., 1986; Yamamoto et al., 1986]. All patients in group A with dermatoglyphic analysis had abnormal findings, the most common being an excess of whorls. Two patients with proximal deletions had tracheo-esophageal fistula [McNeal et al., 1977; Rose et al., 1992]. This has not been reported with more distal 6q deletions.

Proximal deletions of 6q were also notable for lower incidence of several findings when compared to patients with more distal deletions. Microcephaly was seen in 38% of group A patients, but in 83% of patients in the other two groups. Similarly, micrognathia was seen in 36% of proximal deletions, and in 67% of more distal deletions.

Congenital heart malformations were slightly less common in the proximal group (28% versus 49%). This becomes more striking when distinguishing the types of malformation. Only 4 patients in group A had heart malformations [Liberfarb et al., 1978; McLeod et al., 1990; Roland et al., 1993; Warburg et al., 1991]. All had a single isolated lesion (2 patent ductus arteriosus, 1 atrial septal defect, 1 ventricular septal defect). Of 45 patients with more distal deletions 21 had congenital heart disease; 15 were complex lesions representing a wide variety of malformations.

Turleau et al. [1988] have previously summarized the findings in 6 cases of interstitial deletions of the long arm of chromosome 6. The phenotype consisted of round face, upslanting palpebral fissures, hernias, malpositioned feet, excess whorls on finger tips, and severe mental retardation. Our findings agree with those of Turleau et al. Some of the patients included in the paper by Turleau were put into group B in this report.

Deletions: 6q15 to 6q25 (Group B)

Nineteen patients, including case 2, had deletions with both breakpoints between 6q15 and 6q25 [Bzdúch and Lukacová, 1989; Chery et al., 1989; Cote et al., 1981; Fryns et al., 1991; Glover et al., 1988; Horigome et al., 1991; Matkins et al., 1985; McLeod et al., 1990; Nakagome et al., 1980; Narahara et al., 1991; Pandya et al., 1995; Park et al., 1988; Schwartz et al., 1984; Schinzel, 1984; Villa et al., 1995; Wakahama et al., 1991; Yamamoto et al., 1986]. There was a surprising excess of males in this group, 68% compared to 55% in

groups A and C. Seventeen of 22 patients with deletions overlapping the region between 6q21 and 6q23 were male. Intrauterine growth retardation was seen in 60% of group B patients compared to 28% of patients with other 6q deletions. A high, arched palate was noted in 70% of group B patients, but in only 33% of other patients. Hypertelorism was seen in 61% of group B versus 30% of non-group B patients. Twelve of 15 patients with deletions between 6q16 to 6q22 were hyperteloric. Chronic respiratory illness, apnea, or other abnormalities of respiratory control were described in 42% of this group; respiratory abnormalities were described in only 21% of other 6q deletions. The facial appearance was quite different from those with more proximal deletions (Figs. 3, 4). The prominent forehead, microcephaly, micro/retrognathia, short palpebral fissures, and prominent nose seen in case 2 are typical. There is an apparent excess of infant mortality in group B. Five of 19 liveborn infants in group B died before their first birthday [Horigome et al., 1991; Nakagome et al., 1980; Pandya et al., 1995; Schinzel, 1984; Wakahama et al., 1991]. In contrast only 2 patients with terminal deletions died in infancy, one of whom had a very large deletion extending to 6q21 [Ito et al., 1989; Valtat et al., 1992]. One patient in group B had a laryngeal cleft; another had duodenal atresia [Pandya et al., 1995].

Deletions: 6q25 to 6qter (Group C)

Including case 3 we analyzed findings in 26 patients with terminal deletions of 6q [Bartoshesky et al., 1978; Dallapiccola et al., 1978; Fryns et al., 1986; Goldberg et al., 1980; Hagameijer et al., 1977; Ito et al., 1989; Kassikoff and Sekhon, 1990; Kueppers et al., 1977; Liberfarb et al., 1978; McLeod et al., 1990; Meng et al., 1992; Milošević and Kaličanin, 1975; Narahara et al., 1991; Oliveira-Duarte et al., 1990; Rivas et al., 1986; Scarsbrough et al., 1984; Shen-Schwartz et al., 1984; Stevens et al., 1988; Tajara et al., 1990; Tranebjaerg et al., 1986; Valtat et al., 1992]. Eight patients had breakpoints proximal to 6q25. These cases had phenotypic as well as cytogenetic overlap with group B [Dallapiccola et al., 1978; Fryns et al., 1986; Goldberg et al., 1980; Ito et al., 1989; Kueppers et al., 1977; Meng et al., 1992; Shen-Schwartz et al., 1989; Tajara et al., 1990]. There was an increased frequency of breakpoints at 6q25 (13 patients) [Bartoshesky et al., 1978; Kassikoff and Sekhon, 1990; Liberfarb et al., 1978; Meng et al., 1992; Milošević and Kaličanin, 1975; Oliveira-Duarte et al., 1990; Rivas et al., 1986; Stevens et al., 1988; Valtat et al., 1992]. Five patients had terminal deletions with breakpoints distal to 6q25 [Hagameijer et al., 1977; McLeod et al., 1990; Narahara et al., 1991; Scarsbrough et al., 1984; Tranebjaerg et al., 1986]. We considered deletions including portions of 6q27 to be essentially terminal although for some deletions this was not technically true.

Minor anomalies commonly noted in group C included microcephaly, broad nasal tip, prominent nasal bridge, epicanthic folds, and short palpebral fissures that may slant up or down. There were several important defects that, although rare, were seen primarily in group C. Five of 6 patients with cleft palate had terminal deletions [Bartoshesky et al., 1978; Goldberg et al., 1980; Meng et al., 1992; Shen-Schwartz et al., 1989; Warman et al., 1993; Yamamoto et al., 1986]. Three patients with club foot were in this group [Milošević and Kaličanin, 1975; Oliveira-Duarte et al., 1990; Tajara et al., 1990].

Retinal abnormalities were reported in 6 of 9 patients with terminal deletions of 6q who had documented fundoscopic evaluations [Dallapiccola et al., 1978; Hagameijer et al., 1977; McLeod et al., 1990; Meng et al., 1992; Narahara et al., 1991; Rivas et al., 1986; Stevens et al., 1988; Tranebjaerg et al., 1986]. One patient with a proximal deletion was found to have ocular albinism [Rose et al., 1992]. No other patients had documented retinal abnormalities. Warburg et al. recommended thorough ophthalmologic evaluation of all patients with terminal deletion of 6q.

Terminal deletions of 6q were associated with seizures in 38% cases, compared to only 14% in group B and none in group A. Three of 4 patients with hydrocephalus were in group C [Narahara et al., 1991; Roland et al., 1993; Shen-Schwartz et al., 1989]. Brain abnormalities, especially cerebral atrophy, were seen in all groups, but more often in group C (67%) than in groups A and B (33% and 57%, respectively). In addition, 30% of group C patients had an abnormal hair pattern, a marker for abnormal brain development. Only 2 patients from groups A and B have been reported with this finding [Wakahama et al., 1991]. Low anterior or posterior hair line was not included as an abnormal hair pattern.

Cryptorchidism was common in groups B and C. In group C cryptorchidism was frequently accompanied by genital hypoplasia. Three females had labial hypoplasia [Fryns et al., 1986; Oliveira-Duarte et al., 1990; Stevens et al., 1988]; 4 males had micropenis [Bartoshesky et al., 1978; Ito et al., 1989; Milošević and Kaličanin, 1975; Narahara et al., 1991]. One patient in group B had labial hypoplasia [Pandya et al., 1995]. One patient in group A was reported to have micropenis [Gershoni-baruch et al., 1996]. We suspect a gene important for genital development may be located in the terminal region of 6q. Two patients with terminal deletions had diaphragmatic hernia [Kassikoff and Sekhon, 1990; Schwartz et al., 1984], 2 had intestinal malrotation [Milošević and Kaličanin, 1975; Slater et al., 1987], and 3 patients (including case 3) had hepatomegaly [Hagameijer et al., 1977; McLeod et al., 1990]. Two patients in group C had a single umbilical artery [Kassikoff and Sekhon, 1990; Schwartz et al., 1984]. None of these findings were reported in the other 2 groups.

A review of our three patients combined with 57 previous reports of 6q deletions enables one to distinguish 3 distinct phenotypes that correspond to proximal (6q11 to q16), middle (6q15 to q25), and terminal deletions (6q25 to 6qter). Proximal deletions were distinguished by upslanting palpebral fissures, thin lips, umbilical and inguinal hernias, and an increase in whorls on finger tips. They had a relatively lower incidence of microcephaly, micrognathia, and congenital heart dis-

ease. Middle 6q deletions (6q15 to q25) had an excess of males, increased prevalence of low birth weight, hypertelorism, high arched palate, abnormal respiratory control, upper limb malformations, and high infant mortality. Terminal deletions were associated with risk for retinal abnormalities, genital hypoplasia, cleft palate, hydrocephalus, and seizures. All deletions of 6q were associated with mental retardation. Most patients had hypotonia, ear anomalies, and growth failure. This information will be useful in counseling families and giving prognostic information concerning patients with 6q deletions.

A detailed data base including findings reported for all patients reviewed in this report is available from the authors on request.

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